The modification of the Pictet–Spengler reaction proposed by Kametani and Fukumoto [1] has proved to be a convenient method for the synthesis of hydroxy-containing derivatives of tetrahydroisoquinoline that are of interest as potential biologically active and medicinal substances. However, in a number of cases, particularly when primary hydroxyphenylethylamines are used as the starting substances, the yields of the desired products are low because of the necessity for thorough purification to remove significant amounts of impurities. To avoid this, it was recently proposed [2] that the intermediates, viz., the Schiff bases of the hydroxyphenylethylamines with carbonyl compounds, be isolated prior to cyclization; however, this cannot always be accomplished, and this method does not always give positive results.

The utilization of a benzyl group to protect the amino group in the starting hydroxyphenylethylamine, which can be easily removed after the cyclization step, may serve as one of the possible ways to simplify this reaction. Thus the corresponding 1-aryl-2-benzyl-1,2,3,4-tetrahydroisoquinoline-4,6-diones (IIa–c) were synthesized by the reaction of 1-(3-hydroxyphenyl)-2-benzylaminoethanol with aldehydes.

The debenzylation of IIa–c was carried out by hydrogenation over palladium black without pressure at room temperature in aqueous alcohol in, where necessary, an acidic or alkaline medium.
The reaction of I with opianic acid proceeds smoothly and gives tetrahydroisoquinoline IVa. When we used the unsubstituted amine, we were unable to isolate an individual substance from the reaction mixture.

Lactam VI was obtained instead of the expected acid V in the debenzylation of acid IVa in an aqueous alcohol medium. Removal of the benzyl protective group by catalytic hydrogenation in the presence of sodium bicarbonate led to acid V, which was converted to lactam VI by heating with hydrochloric acid. The formation of a lactam was also observed in the catalytic debenzylation of the hydrochloride of ethyl ester IVb, which was obtained by condensation of amine I with ethyl opianate or by esterification of acid IVa in the presence of dicyclohexylcarbodiimide.

The UV spectrum of VI differs substantially from the spectrum of starting acid IVa: instead of the maximum at 285 nm, one observes three absorption maxima at 278, 288, and 303 nm; this can be explained by the greater planarity of resulting lactam VI as compared with IVa. The IR spectrum of lactam contains an intense absorption band of a carbonyl group at 1668 cm⁻¹, which differs appreciably from the analogous bands of acid IVa (1610 cm⁻¹), which has a betaine structure, and the hydrochloride of IVa (1710 cm⁻¹). The ease of formation of a lactam ring in tetrahydroisoquinolines was previously observed in the reaction of 3-hydroxyphenylethylamine with levulinic or ketoglutaric acid [3].

As a consequence of the low solubility of lactam VI in organic solvents, attempts to reduce it by means of diborane and lithium aluminum hydride were unsuccessful.

In the case of the reaction with formaldehyde we demonstrated that benzylated amine I also reacts smoothly with aliphatic aldehydes. In this case we isolated two isomers that are products of ortho and para cyclization (with respect to the phenolic hydroxy group), via., 2-benzyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (VII) and 2-benzyl-1,2,3,4-tetrahy-